Detection of glutamate and glutamine by RF suppression and TE optimization at 7T

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Target audience: Scientists and clinicians who are interested in measuring glutamate (Glu) and glutamine (Gln) using magnetic resonance spectroscopy (MRS).

Purpose: In vivo measurements of Glu and Gln in the human brain are important for studying many neurological and psychiatric diseases because Glu is a vital link between brain energy metabolism and glutamatergic neurotransmission. Spectral separation of glutamate, glutamine, and other coupled spins at 3T is difficult. Recently, Choi *et al.* [1] proposed to use a TE optimized PRESS (point-resolved spectroscopy) method at 7T to resolve glutamate and glutamine, taking advantage of the chemical shift offset artifact [2,3] to suppress overlapping signals from the aspartyl moiety of NAA. In this work, we propose to suppress spectral interference from the aspartyl moiety of NAA by a selective RF pulse placed at the resonance frequency of the NAA aspartyl CH proton at 4.38 ppm, which alters the J-evolution of the NAA aspartyl CH_2 multiplet at 2.5 ppm. The flip angle of this suppression pulse along with the sub-TEs are optimized for the detection of Gln and Glu.

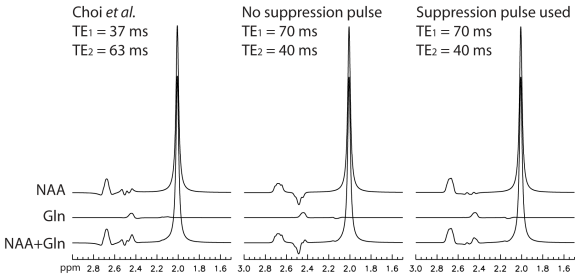

Fig. 1. Numerically simulated NAA, Gln, and NAA+Gln spectra using sub-TEs proposed by Choi *et al.*, our proposed sub-TEs without the suppresion pulse, and our proposed sub-TEs with the suppression pulse. The Gln/NAA ratio was set to be 0.15. The spectra were broadened to 9 Hz.

Methods:

Suppression pulse and TE optimization: A 20 ms sinc-Gauss RF pulse with its frequency targeting 4.38 ppm at 7T was inserted in between the two refocusing pulses of the PRESS sequence. Because the NAA aspartyl CH proton at 4.38 ppm is J-coupled to the NAA aspartyl CH_2 spins at 2.5 ppm, this suppression pulse indirectly affects the NAA multiplet at 2.5 ppm. Different flip angles of the suppression pulse result in different NAA aspartyl CH_2 multiplet signals at 2.5 ppm. In order to find the optimal sequence parameters for Glu and Gln detection, density matrix simulation programs were developed using the GAMMA C++ library to compute the spectra of different metabolites for different values of TE_1, TE_2, and suppression pulse flip angle. It was necessary to use the actual amplitude waveforms of the RF pulses in computing the time evolution of the density operator. The PRESS excitation pulse was an amplitude modulated pulse with a 3.1 kHz bandwidth (full width at half height). The two refocusing pulses were also amplitude-modulated and had a bandwidth of 1.9 kHz [4]. Using these simulations, it was found that TE_1 = 70 ms, TE_2 = 40 ms, and suppression pulse flip angle = 90° resulted in excellent resolution and peak amplitude for Glu, Gln, and GSH, as well as minimal NAA aspartyl CH_2 multiplet signals at 2.5 ppm.

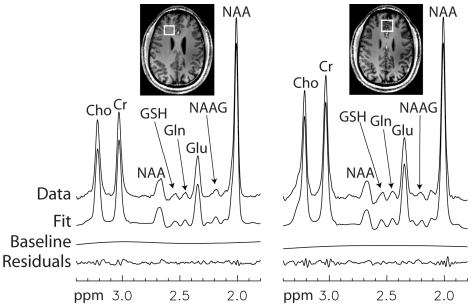

Fig. 2 Linear combination fitting of spectra from the frontal lobe WM and GM regions of a normal volunteer.

In vivo experiments: Four normal volunteers, who gave informed consent in accordance with procedures approved by the local institutional review board, were scanned on a Siemens 7T scanner equipped with a 32-channel receiver head coil. For each subject, two MRS scans were performed, one in frontal lobe white matter (WM) and the other in frontal lobe grey matter (GM). The average voxel volumes in the WM and GM were 12 mL and 18 mL, respectively. The pulse sequence had TR = 2.5 s, TE_1 = 70 ms, TE_2 = 40 ms, suppression pulse flip angle = 90°, suppression pulse bandwidth = 160 Hz, spectral width = 4000 Hz, number of data points = 2048, and number of averages = 128. Water suppression was accomplished using eight frequency-selective RF pulses. In addition, eight interleaved unsuppressed water signals were acquired, one after every 16 water-suppressed acquisitions. The 32-channel data were combined into a single FID (free induction decay) by a generalized least square method. The FID was divided by the phase factor of the unsuppressed water signal for eddy current correction. Metabolite concentrations were quantified by a linear combination fitting program developed in-house with a fitting range of 1.8 - 3.4 ppm.

Results: Three sets of numerically simulated NAA, Gln, and NAA+Gln spectra are plotted in Fig. 1. The first set of spectra were computed using sub-TEs proposed by Choi *et al.* The second set of spectra were computed using our proposed sub-TEs but without using the suppression pulse. The NAA multiplet at 2.5 pmm has a relatively large negative peak, which makes Gln detection difficult. Small errors in modeling the NAA aspartyl CH_2 multiplet would result in large errors in Gln quantification. For the third set of spectra, the suppression pulse was used along with the proposed sub-TEs. The NAA multiplet is minimized compared to the Gln peak, which greatly benefits accurate quantification of Gln. The reconstructed spectra and fitting results for one volunteer are plotted in Fig. 2. It can be seen that both spectra have excellent resolution for Gln and Glu detection. The Gln and Glu multiplets are fitted very well by a linear combination of density matrix simulated basis spectra. The mean metabolite concentrations of the four normal volunteers are given in Table 1. The Cramer-Rao lower bound (CRLB) for each metabolite was also computed.

Discussion: The suppression pulse used in this work is reminiscent of the widely used J-editing pulses. However, the suppression pulse is not used to edit the signal of the metabolite of interest as in two-step J-editing. Instead, the suppression pulse is used to suppress unwanted signal in a single shot through complex J-coupling interactions without affecting the signals of metabolites of interest (Glu and Gln). In the case of the aspartyl moiety of NAA, there is a large difference between $J_{H2\text{-}H3}$ (3.9 Hz) and $J_{H2\text{-}H3'}$(9.8 Hz), as well as a large $J_{H3\text{-}H3'}$ (-15.6 Hz) [5]. The overall action of the suppression pulse effectively minimizes contribution from the NAA aspartyl CH_2 multiplet around 2.5 ppm. This approach may also be used for detecting other strongly coupled metabolite signals.

Table 1. Mean metabolite ratios in the frontal lobe WM and GM regions of four normal volunteers.

	Frontal lobe WM		Frontal lobe GM	
	Metabolite ratios (/[Cr])	CRLB (%)	Metabolite ratios (/[Cr])	CRLB (%)
Cr	1.0	0.54±0.07	1.0	0.35±0.07
Cho	0.35±0.03	0.54±0.06	0.28±0.02	0.41±0.08
NAA	2.1±0.2	0.41±0.04	1.5±0.2	0.33±0.08
NAAG	0.42±0.09	1.0±0.2	0.12±0.04	3±1
Glu	1.23±0.08	0.78±0.08	1.4±0.1	0.46±0.07
Gln	0.20±0.05	6.0±0.9	0.26±0.03	2.8±0.3
GSH	0.19±0.02	4.5±0.9	0.19±0.03	2.9±0.4

Conclusion: Density matrix simulations and in vivo experiments have demonstrated that using a J suppression pulse with TE optimization minimizes the NAA aspartyl CH_2 multiplet signal at 2.5 ppm, leading to improved accuracy and precision of Gln quantification with simultaneous measurement of glutamate.

References

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